UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

July 16, 2001

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 72674-EA / Densil DG
DP Barcode: D274449
Case No: 070296

To: Marshall Swindell, PM 33 / Martha Terry
Regulatory Management Branch
Antimicrobials Division (7510C)

From: Ian Blackwell, Biologist
Efficacy Evaluation Team
Product Science Branch
Antimicrobials Division (7510C)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

7/18/01

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

Applicant: Avecia, Inc.

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
N-Butyl-1,2-benzisothiazolin-3-one	45
Other Ingredient(s):	55
Total:	100%

BACKGROUND: Avecia, Inc., has submitted a set of four acute toxicity studies to support the acute toxicity requirements for their product "Densil DG". This package is lacking the acute inhalation toxicity and primary eye irritation studies that would make it a complete set or "six-pack". The studies were conducted by Zeneca Biocides' Central Toxicology Laboratory. The MRID Numbers are 453809-08 through 453809-11. These studies received a primary review from the EPA contractor Oak Ridge Laboratories. PSB/AD conducted a brief secondary review of these studies to be sure that they do meet OPP/EPA guidelines.

RECOMMENDATIONS: PSB findings are:

1. MRID Number 453809-08: The acute oral toxicity study is acceptable.

2. MRID Number 453809-9: The acute dermal toxicity study is acceptable.

3. MRID Number 453809-10: The primary skin irritation study is acceptable.

   Note: The reviewer would like to note that this study had some additional aspects to its methodology. This study also made a dose application for three minutes and another for one hour in addition to the standard four hour exposure. Even after a brief three minute exposure to the test material, moderate/severe erythema was seen up to nine days after treatment with the test material. These are simple notes on this study and do not affect the outcome of the study in any way except to enforce the toxicity category I assigned to this product.

4. MRID Number 453809-11: The dermal sensitization study is acceptable and shows the product to be a strong sensitizer.

5. No primary eye irritation study was included with this submission. However, if the registrant desires, PSB/AD will waive the requirement for the primary eye irritation study and assign the product based upon the toxicity category I assignment and corrosive effects of the product observed in the primary skin irritation study. If the registrant feels that this product would be improperly served by assigning the primary eye irritation study a toxicity category I, they must submit another study to demonstrate that this product should be placed into another toxicity category.

6. No acute inhalation study was submitted for this product, nor was the reason for the absence of this study given. The registrant must address the requirement for the acute inhalation toxicity study for this product.

7. NOTE: Although each of these studies was properly conducted and classified as acceptable, the test material used in each of these studies is identified as "DS 6039", and not the registration product. In order for these studies to be accepted, the registrant must

identify the DS 6039 and its relationship to the registration product. (That is, is DS 6039 actually Densil DG?)

The acute toxicity profile for File Symbol 72674-EA is currently:

acute oral toxicity	unacceptable
acute dermal toxicity	unacceptable
acute inhalation toxicity	unacceptable
primary eye irritation	unacceptable
primary skin irritation	unacceptable
dermal sensitization	unacceptable

The acute toxicity profile for this product cannot be compiled until the registrant has done the following:

A. Identified the test material and its relationship to EPA File Symbol 72674-EA.
B. Addressed the missing acute inhalation toxicity study.
C. State how they plan to address the missing primary eye irritation study. (For this the registrant may accept the data waiver offered in number 5 above.)

LABELING:

No precautionary labeling can be recommended for this product until the acute toxicity profile is compiled.

DATA EVALUATION RECORD

DS 6039
(1,2-BENZISOTHIAZOLIN-3-ONE, 2-BUTYL)

STUDY TYPE: ACUTE ORAL TOXICITY - RAT [870.1100 (§81-1)]
MRID 45380908

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K294

Primary Reviewer:
Gary A. Sega, Ph.D.

Signature: Gary Sega
Date: JUN 27 2001

Secondary Reviewers:
H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.

Signature: HT Borges
Date: JUN 27 2001

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: JUN 27 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: JUN 27 2001

Disclaimer

This review may have been altered subsequent to the contractor's signatures above.

Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC., for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: I. Blackwell, M.S. Date: 7/16/01

EPA Work Assignment Manager: Bonaventure Akinlosotu, Ph.D. Date:_____
Antimicrobial Division (9510C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Toxicity - Rat [OPPTS 870.1100 (§81-1)]

DP BARCODE: D274449 SUBMISSION CODE: S596267
P.C. CODE: 098951 CASE NO.: 070296

TEST MATERIAL: DS 6039

SYNONYMS: 1,2-Benzisothiazolin-3-one, 2-butyl-, 45.2% a.i.

CITATION: Johnson, I.R. (1997) DS 6039: Acute oral toxicity to the rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Laboratory Project ID: Report No.: CTL/P/5618, Study No.: AR6466, October 16, 1997. MRID 45380908. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897.

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 45380908) Alpk:AP$_f$SD rats, were gavaged with DS 6039 (Batch#: 151694, 45.2% a.i.). Five males/group received doses of 2000 and 5000 mg/kg and five females received a dose of 5000 mg/kg. Surviving animals were observed for 14 days.

No male rats from the 2000 mg/kg group died while all males in the 5000 mg/kg group died or were killed *in extremis* on day 1. One female showed signs of moderate toxicity and was found dead on day 10. All other females survived until the end of the study. Males in the 2000 mg/kg group showed mild signs that included decreased activity, upward curvature of the spine and diarrhea, all of which cleared by day 2. All females showed various signs that included decreased activity, dehydration, piloerection, salivation,upward curvature of the spine, stains around nose and mouth and urine stains. All surviving animals showed an overall weight gain during the study

The oral LD_{50} for males was 3162 mg/kg; for females it was >5000 mg/kg.

DS 6039 is in TOXICITY CATEGORY III.

This study is classified as **Acceptable/Guideline** for an acute oral toxicity study [870.1100 (§81-1)] in the rat.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: DS 6039

Description: brown liquid
Batch#: 151694
Composition: 45.2% a.i. in formulation inactive ingredients: 54.8%
CAS No.: 4299-07-4 (1,2-Benzisothiazolin-3-one, 2-butyl-)

2. Vehicle and/or positive control: corn oil

3. Test animals

Species: rat
Strain: Alpk:AP$_f$SD
Age and weight at dosing: 8 - 12 weeks old; males:303 - 367 g; females: 215 - 238 g
Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
Acclimation period: 6 days or more
Diet: R&M No. 1 (Special Diet Services Limited, Witham, Essex, UK), *ad libitum,* except the night prior to dosing
Water: mains water, *ad libitum*
Housing: housed by sex in groups of 5 in cages suitable for animals of this strain and expected weight range
Environmental conditions:
Temperature: 22 $\pm$ 3°C
Relative Humidity: 30 - 70%
Air changes: a minimum of 15 per hour
Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates

Start: May 20, 1997; end: June 12, 1997

2. Animal assignment and treatment

Animals were identified by ear punch and cage card. Before dosing, the rats were examined to ensure their normalcy. The test material was dissolved in corn oil and a standard volume of 10 mL/kg was administered by oral gavage using a stomach tube or intubation cannula. Five males received a dose of 2000 mg/kg and 5 males and 5 females received a dose of 5000 mg/kg. The animals were observed for signs of systemic toxicity twice, following dosing on day 1, and subsequently observed daily up to day 15. Any rats *in extremis* were killed and

necropsied and any rats found dead were also necropsied as soon as possible after death. All rats surviving to day 15 were killed and necropsied. Animals were weighed prior to fasting (day -1), immediately before dosing (day 1) and on days 8 and 15.

3. Statistics

The oral LD_{50} for the males was estimated from the mortality data (including animals killed *in extremis*) by linear log-dose interpolation using nominal dose values.

II. RESULTS AND DISCUSSION

A. MORTALITY

Following the dose of 2000 mg/kg no male rats died. Following the dose of 5000 mg/kg all the males showed signs of extreme toxicity and one was found dead; the others were all killed *in extremis* on day 1. One female showed signs of moderate toxicity and was found dead on day 10. All other females survived until the end of the study. The oral LD_{50} was estimated to be 3162 mg/kg to male rats and was considered to be greater than 5000 mg/kg to female rats. This places DS 6039 in TOXICITY CATEGORY III.

B. CLINICAL OBSERVATIONS

Following a dose of 2000 mg/kg to male rats, signs of slight systemic toxicity were seen in all animals with complete recovery by day 2. Signs included one or more of the following: decreased activity, upward curvature of the spine and diarrhea. Following the dose of 5000 mg/kg all females showed various signs that included decreased activity, dehydration, piloerection, salivation, upward curvature of the spine, stains around nose and mouth and urine stains. Four of the five females survived to the end of the study.

C. BODY WEIGHT

All surviving animals showed an overall weight gain during the study.

D. NECROPSY

One male from the 2000 mg/kg group and all the males and two females (one found dead and one that survived to termination) from the 5000 mg/kg group showed changes to the stomach and stomach contents, together with (in some animals) fluid and adhesions in the abdominal cavity which were considered to be effects of the test material. All other findings were not considered to be compound-related. No abnormalities were seen in the rats surviving to 14 days. In rats that died from the treatment, hemorrhages of the thymus and stomach and dark reddish lungs were observed.

E. DEFICIENCIES

None noted.

DATA EVALUATION RECORD
DS 6039
(1,2-BENZISOTHIAZOLIN-3-ONE, 2-BUTYL)

STUDY TYPE: ACUTE DERMAL TOXICITY - RAT [870.1200 (§81-2)]
MRID 45380909

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K294

Primary Reviewer: Gary A. Sega, Ph.D.	Signature: Date:	Gary Sega JUN 27 2001
Secondary Reviewers: H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.	Signature: Date:	H T Borges JUN 27 2001
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross JUN 27 2001
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L. A. Wilson JUN 27 2001

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Oak Ridge National Laboratory managed and operated by UT-Battelle, LLC, for the U.S. Department of Energy under Contract No. DE-AC05-00OR22725.

EPA Reviewer: Ian Blackwell, M.S. Date: 7/16/01

EPA Work Assignment Manager: Bonaventure Akinlosotu, Ph.D. Date:_____
Antimicrobial Division (9510C)

DATA EVALUATION RECORD

STUDY TYPE: Acute Dermal Toxicity - Rat [OPPTS 870.1200 (81-2)]

DP BARCODE: D274449 SUBMISSION CODE: S596267
P.C. CODE: 098951 CASE NO.: 070296

TEST MATERIAL: DS 6039

SYNONYMS: 1,2-Benzisothiazolin-3-one, 2-butyl-, 45.2% a.i.

CITATION: Johnson, I.R. (1997) DS 6039: Acute dermal toxicity to the rat. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Laboratory Project ID: Report No.: CTL/P/5619, Study No.: CR3381, September 19, 1997. MRID 45380909. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897.

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 45380909) Alpk:AP$_f$SD (Wistar-derived) rats were dermally exposed to 2000 mg/kg of DS 6039 (Batch#: 151694, 45.2% a.i.) in a Limit Test, using 5 animals/sex. Animals were observed for 14 days.

No deaths were seen during the study. Signs of slight systemic toxicity were seen for one female with complete recovery by day 4. Signs of moderate or extreme skin irritation were seen on all animals during the study which persisted on all males and 4 females to the end of the study. One male and one female failed to gain weight during the study while remaining animals gained weight. Three males and two females showed scabs at the application site and one of these males also showed skin thickening. These findings were considered compound-related.

The dermal LD_{50} for males, females and combined was >2000 mg/kg. This places DS 6039 in TOXICITY CATEGORY III.

This study is classified as **Acceptable/Guideline** for an acute dermal toxicity study [870.1200 (81-2)] in the rat.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: DS 6039

   Description: brown liquid
   Batch#: 151694
   Composition: 45.2% a.i. in formulation inactive ingredients: 54.8%
   CAS No.: 4299-07-4 (1,2-Benzisothiazolin-3-one, 2-butyl-)

2. Vehicle and/or positive control: none

3. Test animals

   Species: rat
   Strain: Alpk:AP$_f$SD
   Age and weight at dosing: 8 - 12 weeks old; males:318 - 386 g; females: 213 - 247 g
   Source: Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK
   Acclimation period: 6 days or more
   Diet: R&M No. 1 (Special Diet Services Limited, Witham, Essex, UK), *ad libitum*
   Water: mains water, *ad libitum*
   Housing: housed individually in cages suitable for animals of this strain and expected weight range
   Environmental conditions:
   Temperature: approximately 22 ± 3°C
   Relative Humidity: 30 - 70%
   Air changes: a minimum of 15 per hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: May 7, 1997; end: May 21, 1997

2. Animal assignment and treatment

   Animals were identified by ear punch and cage card. Before dosing, the rats were examined to ensure their normalcy. Five males and 5 females were given a dermal exposure of 2000 mg/kg (Limit Dose). The backs of the animals were clipped 16 to 32 hours before dosing and the undiluted test material was applied at 2 mL/kg to the clipped backs, covered with gauze and a plastic film and held in place with an adhesive bandage and PVC tape. After 24 hours the wrappings were removed and the skin wiped with wet cotton wool to remove any remaining

test material and dried with clean tissue paper. The animals were observed twice between one and five hours after application for gross abnormalities. Subsequent observations for signs of systemic toxicity and skin irritation were made daily up to day 15. The animals were weighed prior to dosing on day 1, and on days 8, and 15. All rats were sacrificed on day 15 and subjected to external observation and examination of all thoracic and abdominal viscera. All abnormalities were recorded but tissues were not submitted for histopathological examination.

3. Statistics

Calculation of the dermal LD_{50} was not required.

II. RESULTS AND DISCUSSION

A. MORTALITY

No animals died during the study. Therefore, the dermal LD_{50} was higher than 2000 mg/kg for males, females and combined. This places DS 6039 in TOXICITY CATEGORY III for an acute dermal exposure in the rat.

B. CLINICAL OBSERVATIONS

Signs of slight systemic toxicity were seen from one female with complete recovery by day 4. Minor clinical signs in two other animals were those commonly seen in dermal toxicity studies and were not considered compound-related. Signs of moderate or extreme skin irritation were seen on all animals during the study which persisted to the end of the study on all males and 4 females. The remaining female showed signs of possible necrosis.

C. BODY WEIGHT

One male and one female failed to gain weight during the study. All other animals gained weight.

D. NECROPSY

Three males and two females developed scabs at the application site and one of these males also showed skin thickening. These findings were considered compound-related. The possible necrosis seen on one female was not confirmed at necropsy. No macroscopic abnormalities were seen in the remaining animals.

E. DEFICIENCIES

There was a significant decrease in animal room temperature from nominal (18°C). It is unlikely that this would have affected the study results.

DATA EVALUATION RECORD
DS 6039
(1,2-BENZISOTHIAZOLIN-3-ONE, 2-BUTYL)

STUDY TYPE: PRIMARY DERMAL IRRITATION - RABBIT [870.2500 (§81-5)]
MRID 45380910

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K294

Primary Reviewer:
Gary A. Sega, Ph.D.

Signature: Gary Sega
Date: JUN 27 2001

Secondary Reviewers:
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Signature: H T Borges
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Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: JUN 27 2001

Quality Assurance:
Lee Ann Wilson, M.A.

Signature: L. A. Wilson
Date: JUN 27 2001

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EPA Reviewer: Ian Blackwell, M.S. Date: 7/16/01

EPA Work Assignment Manager: Bonaventure Akinlosotu, Ph.D. Date:_____
Antimicrobial Division (9510C)

DATA EVALUATION RECORD

STUDY TYPE: Primary Dermal Irritation - Rabbit [OPPTS 870.2500 (§81-5)]

DP BARCODE: D274449 SUBMISSION CODE: S596267
P.C. CODE: 098951 CASE NO.: 070296

TEST MATERIAL: DS 6039

SYNONYMS: 1,2-Benzisothiazolin-3-one, 2-butyl-, 45.2% a.i.

CITATION: Johnson, I.R. (1997) DS 6039: Skin irritation to the rabbit. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Laboratory Project ID: Report No.: CTL/P/5620, Study No.: EB4611, October 6, 1997. MRID 45380910. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897.

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 45380910) a single female New Zealand White rabbit was dermally exposed for 3 minutes, 1 hour and 4 hours to 0.5 mL of undiluted DS 6039 (Batch#: 151694, 45.2% a.i.) applied to three intact skin sites that had been clipped free of hair. Each site was scored for erythema and edema according to the Draize method daily for 8 - 10 days following the end of exposure. All exposure times produced slight to severe erythema and edema that persisted for up to 10 days, respectively. After the 4 hour exposure, well-defined erythema was seen for 5 days and moderate to severe erythema was seen from 6 to 8 days. Severe edema was seen 1 hour after decontamination and was slight to moderate from 1 to 3 days. Additional signs seen with one or more of the exposures included scabbing, thickening, wrinkling, hardening of the skin, desquamation, blanching and necrosis.

In this study, DS 6039 was classified as corrosive to rabbit skin. The TOXICITY CATEGORY is I for primary dermal irritation.

This study is classified as **Acceptable/Guideline** and satisfies guideline requirements for a primary dermal irritation study [870.2500 (§81-5)] in the rabbit.

COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: DS 6039

Description: brown liquid
Batch#: 151694
Composition: 45.2% a.i. in formulation inactive ingredients: 54.8%
CAS No.: 4299-07-4 (1,2-Benzisothiazolin-3-one, 2-butyl-)

2. Vehicle and/or positive control: none

3. Test animals

Species: rabbit
Strain: New Zealand White albino
Age and weight at dosing: female: young adult, 3.88 kg
Source: Charles River UK Limited, Margate, Kent, UK
Acclimation period: 6 days or more
Diet: STANRAB SQC, Special Diet Services Limited, Stepfield, Witham, Essex, UK, *ad libitum*
Water: mains water, *ad libitum*
Housing: housed in a cage suitable for animals of this strain and expected weight range
Environmental conditions:
Temperature: 17 ± 3°C
Relative Humidity: 30 - 70%
Air changes: a minimum of 15 per hour
Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates

Start: April 18, 1997; end: April 29, 1997

2. Animal assignment and treatment

One female rabbit was identified by ear marking and cage card. The right and left flanks were clipped 24 hours before treatment and undiluted test material (0.5mL) was applied for 3 min to the bottom left flank, for 1 hour to the top right flank, and for 4 hours to the top left flank 3 days later. Treated areas were covered with gauze, secured with surgical tape, covered with impermeable rubber sheeting and secured with impermeable polyethylene adhesive tape. At the end of each exposure, the wrapping was removed, the skin wiped with wet

cotton wool to remove any remaining test material and dried with clean tissue paper. The treated sites were scored daily for up to 10 days following the end of exposure for erythema and edema according to the Draize method.

II. RESULTS AND DISCUSSION

A. The animal showed no signs of ill-health during the study. After the 3 minute exposure, erythema was slight to moderate to severe from 2 hours to 9 days. Slight to severe edema was seen from 2 hours to 3 days. Additional signs, seen for 10 days, included thickening, wrinkling and hardening of the skin, blanching and necrosis. After the 1 hour exposure, erythema was slight to moderate to severe for 10 days. Edema was seen for 6 days. Additional signs, seen for 10 days, included desquamation, thickening, wrinkling and hardening of the skin, blanching and possible necrosis. After the 4 hour exposure, well-defined erythema was seen for 5 days (average Draize score=2.0) and moderate to severe erythema was seen from 6 to 8 days. Severe edema was seen 1 hour after decontamination and was slight to moderate from 1 to 3 days (average Draize score=2.7). Additional signs included scabbing, thickening and wrinkling of the skin.

DS 6039 was classified as corrosive to rabbit skin. The TOXICITY CATEGORY is I.

B. DEFICIENCIES

None noted.

DATA EVALUATION RECORD
DS 6039
(1,2-BENZISOTHIAZOLIN-3-ONE, 2-BUTYL-)

STUDY TYPE: DERMAL SENSITIZATION - GUINEA PIG [870.2600 (§81-6)]
MRID 45380911

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
Chemical Hazard Evaluation Group
Toxicology and Risk Analysis Section
Life Sciences Division
Oak Ridge National Laboratory
Oak Ridge, TN 37831
Action No. K294

Primary Reviewer: Gary A. Sega, Ph.D.	Signature: Date:	Gary Sega JUN 27 2001
Secondary Reviewers: H. Tim Borges, M.T.(A.S.C.P.), Ph.D., D.A.B.T.	Signature: Date:	HT Borges JUN 27 2001
Robert H. Ross, M.S., Group Leader	Signature: Date:	Robert H. Ross JUN 27 2001
Quality Assurance: Lee Ann Wilson, M.A.	Signature: Date:	L. A. Wilson JUN 27 2001

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EPA Reviewer: Ian Blackwell, M.S. Date: 7/16/01

EPA Work Assignment Manager: Bonaventure Akinlosotu, Ph.D. Date:_____
Antimicrobial Division (9510C)

DATA EVALUATION RECORD

STUDY TYPE: Dermal Sensitization - Guinea Pig [OPPTS 870.2600 (§81-6)]

DP BARCODE: D274449 SUBMISSION CODE: S596267
P.C. CODE: 098951 CASE NO.: 070296

TEST MATERIAL: DS 6039

SYNONYMS: 1,2-Benzisothiazolin-3-one, 2-butyl-, 45.2% a.i.

CITATION: Johnson, I.R. (1997) DS 6039: Skin sensitization to the guinea pig. Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, UK SK10 4TJ. Laboratory Project ID: Report No.: CTL/P/5621, Study No.: GG6967, October 6, 1997. MRID 45380911. Unpublished.

SPONSOR: Zeneca Biocides, Wilmington, DE 19897.

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 45380911) with DS 6039 (Batch#: 151694, 45.2% a.i.), 30 female Albino Dunkin Hartley guinea pigs were tested using the Buehler method, with 20 animals in the test group and 10 in the control group.

The induction phase used three weekly dermal exposures to 0.4 mL of undiluted test material (test group) or a dry bandage (control group). At challenge, a 50% and 25% concentration of the test material in corn oil was applied to the left and right flanks, respectively, of all animals for at least 6 hours. Challenge sites exposed to 50% test material showed scattered mild redness (score=1) or moderate and diffuse redness (score=2) at the 1 and/or 2 day observation times in 15/20 and 1/10 test and control animals, respectively, for a net response of 65%. Challenge sites exposed to 25% test material showed scores of 1 or 2 at the 1 and/or 2 day observation times in 12/20 and 0/10 test and control animals, respectively. The net response was 60%. The test material was considered to be a strong dermal sensitizer. The study report included a hexylcinnamaldehyde positive control study that was carried out within 6 months of the present study. The results were appropriate.

Based on the evaluation system used in this study, DS 6039 was a strong dermal sensitizer.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a dermal sensitization study [870.2600 (§81-6)] in the guinea pig.
COMPLIANCE: Signed and dated GLP, Data Confidentiality, Flagging and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: DS 6039

   Description: brown liquid
   Batch No.: 151694
   Composition: 45.2% a.i. in formulation inactive ingredients: 54.8%
   CAS No.: 4299-07-4 (1,2-Benzisothiazolin-3-one, 2-butyl-)

2. Vehicle and/or positive control: corn oil; positive control: hexylcinnamaldehyde

3. Test animals

   Species: guinea pig
   Strain: Albino Dunkin Hartley
   Age and weight at dosing: females: young adults, 330 - 434 g
   Source: David Hall, Newchurch, Burton-on-Trent, Staffs, UK
   Acclimation period: 6 days or more
   Diet: FD1, Special Diet Services, Witham, Essex, UK, *ad libitum*
   Water: mains water, *ad libitum*
   Housing: housed in groups of 5 in cages suitable for animals of this strain and expected weight range
   Environmental conditions:
   Temperature: 20 ± 3°C
   Relative Humidity: 30 - 70%
   Air changes: a minimum of 15 per hour
   Photoperiod: 12 hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates

   Start: April 22, 1997; end: June 22, 1997

2. Animal assignment and treatment

   Animals were identified by waterproof marking on the clipped flank and by cage card. They were induced and challenged according to the Buehler method.

   Induction phase: Twenty test and 10 control animals were clipped free of hair on the scapular region and treated topically with either 0.4 mL of undiluted test material or a dry bandage. The test material was applied on a lint patch, covered with adhesive tape and held in place by adhesive elastic bandage and PVC tape. The dressing was left in place for 6 hours. The induction process was repeated at 7 day intervals on the same sites, for a total of three, 6-hour exposures.

Challenge phase: Fourteen days after the last induction dose, both flanks of each animal were clipped and 0.1 - 0.2 mL of a 50% and a 25% (w/v) preparation of the test material in corn oil were applied to lint patches and then applied to the left and right flanks, respectively. The patches were held in place with impermeable polyethylene tape and left on the animals for at least 6 hours. Following challenge, erythematous reactions were recorded 1 and 2 days after patch removal.

II. RESULTS AND DISCUSSION

A. INDUCTION REACTIONS AND DURATION

Slight to moderate skin irritation was seen on all test animals during the induction phase while no signs of irritation were seen on any control animal.

B. CHALLENGE REACTIONS AND DURATION

Test and control animals: Challenge sites exposed to 50% test material showed scattered mild redness (score=1) or moderate and diffuse redness (score=2) at the 1 and/or 2 day observation times in 15/20 and 1/10 test and control animals, respectively. The net response was 65%. Challenge sites exposed to 25% test material showed scattered mild redness or moderate and diffuse redness at the 1 and/or 2 day observation times in 12/20 and 0/10 test and control animals, respectively. The net response was 60%.

The test material was considered to be a strong dermal sensitizer.

C. POSITIVE CONTROL

The study report included a hexylcinnamaldehyde positive control study that was carried out within 6 months of the present study. The results were appropriate.

D. ADDITIONAL TESTING

It is the reviewer's opinion that the study was conducted in a manner suitable to detect the sensitization potential of the test material. No additional testing is needed.

E. DEFICIENCIES

None noted